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Overview of the Risk of Respiratory Cancer from Airborne Contaminants

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This overview on defining risk of respiratory cancer from airborne pollutants summarizes broad issues related to a number of the environmental agents that are discussed in the articles that follow. Lung cancer kills more than 100,000 people annually and is the major form of cancer in both sexes in middle age. Cigarette smoking is the major cause of respiratory cancer and must be taken into account in any study of the effect of an environmental agent on the risk of respiratory cancer, particularly at relatively low levels of excess risk (RR greater than 1.0 but less than 2.0).

The agents considered in this series all have the potential for widespread community exposures, either because there is widespread long-term exposure (passive smoking), the agents are direct byproducts of energy consumption (organic particles), have ubiquitous production and use patterns (formaldehyde and fibers), or occur widely in natural settings (radon). Several issues—measurement of exposure, latency, confounding factors and bias, extrapolation from animals to humans, population at risk, and attributable risk—*must be considered for each agent. A further issue related to exposure estimates is the relationship* of exposure to actual dose. Understanding exposure some 25 to 40 years in the past is important because of the prolonged latency period in the development of respiratory cancers. To the degree that these agents act synergistically with smoking, the reduction of smoking or of exposure to these agents may have greater public health consequences than would be anticipated from the directly measured attributable risk of each of these agents separately.

Unquestionably, cigarette smoking is the major cause of respiratory cancer. From the very early studies of Doll and his colleagues roughly 30 years ago to the present, almost all investigators would agree that over 90% of lung cancer in men is attributable to cigarette smoking. The figure is only slightly lower in females and, unfortunately, is increasing rapidly. Cigarette smoking also plays a major role for all other respiratory cancers. Thus, the issue for almost all putative environmental agents is whether they are additive or synergistic with cigarette smoking. Other environmental agents must be evaluated in the context of their interaction with cigarette smoking. Because of the overwhelming effect of cigarette smoking, population-based studies that report on environmental effects, particularly at relatively low levels of excess risk (RR greater than 1.0 but less than 2.0), and that do not attempt to take cigarette smoking into account, must be considered seriously flawed. These studies, therefore, can contribute very little to our understanding of risk factors for respiratory cancer.

This overview will not attempt to summarize all of the data on environmental agents believed to be associated with respiratory cancer. Rather, the purpose of this paper is to attempt to summarize some broad issues that may relate to a number of the environmental agents that will be discussed in the papers that follow.

In addition, not every agent that has ever been reported as associated with respiratory cancers will be considered (Table 1). However, there are common themes that apply to most, if not all, of these agents. These agents (except possibly the metals, which may

Table 1. Estimated numbers of persons exposed to agents discussed.

Agents	Occupational exposure	General population exposure
Radon	?	20 million (great uncertainty)
Formaldehyde	1.3 million	2.2 million (mobile homes less than 5 years old) 1.5 million UFFI[a]
Organic particles	3.9 million	20 million (great uncertainty)
Fibers	1.6 million	10 million[b]
Passive *smoking*	*30% of workers*	*70% of household* members
Metals		
Cadmium	1.5 million	?
Arsenic	1.5 million	?

[a] UFFI = urea-formaldehyde foam insulation.
[b] Dose equivalent over a lifetime (70 years) < 1 fiber/cm^3 – year.

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affect only specifically exposed occupational groups) have the potential for widespread community exposures because there is widespread long-term exposure (passive smoking), the agents are direct byproducts of energy consumption (organic particles), have ubiquitous production and use patterns (formaldehyde and fibers), or occur widely in natural settings (radon). In the last 10 years, increasing efforts to conserve energy in some areas have led to reduced ventilation rates indoors. This has resulted in potentially harmful agents, either generated or able to penetrate indoors, reaching higher concentrations than might previously have been expected. If these agents are respiratory carcinogens, a legitimate question can be asked as to whether these concentrations are at a sufficient level to place the general population at increased risk of respiratory cancers.

To explore this question, an assessment must be made of the existing data that support or refute the hypothesis that each of these agents, either acting alone or in combination with cigarette smoking or other agents, is associated with increased risk of respiratory cancer. As is usually the case, data obtained from a variety of disciplines and from levels of exposure that may be considerably higher than might be obtained in community settings must be utilized. Extrapolation of results from animal studies to humans may be required. It must be determined if it is possible to extrapolate from higher levels of exposure to those more commonly associated with community exposures. In fact, for few of these agents is there sufficient information available to make such extrapolations. Questions must be identified and recommendations made to improve the data base so that in the not too distant future risk estimates for the generally exposed populations can be made.

Several issues—measurement of exposure, latency, confounding factors and bias, extrapolation, population at risk, and attributable risk—need to be considered for each of the agents. Although treated separately, many of these issues are intertwined.

Measurement of Exposure

For many, if not most, population-based studies, exposure has been defined by historical data that describe where subjects or patients have lived or worked. As crude as this kind of information is, significant associations have been identified because the spontaneous occurrence of disease is in some instances so infrequent without such exposure. Nasal sinus cancer among nickel workers is one such example. Although suspected as early as 1927, not until 1939 did formal studies in the nickel industry come about. The concern at the time was that relatively rare tumors, nasal and lung cancers, were occurring in a small community dominated by a nickel refining factory and clearly represented an epidemic that required explanation (*1*). In 845 workers, the simple historical information of having worked for 5 or more years before 1929 was associated with at least a 300-fold excess risk of nasal cancer and a 7-fold risk of lung cancer compared to workers with equal durations of employment occurring after 1929 (*2*) (Table 2).

Table 2. Risk of nasal or lung cancer in nickel workers.[a]

Employment period	Risk		Observed/ expected
	Observed	Expected	
Nasal cancer			
Before 1925	39	0.107	364
1925–29	0	0.014	—
1930–44	0	0.022	—
Lung cancer			
Before 1925	105	13.94	7.5
1925–29	4	2.27	1.3
1930–44	4	3.79	—
Other cancers			
Before 1925	49	31.50	1.6
1925–29	3	3.67	1.00
1930–44	6	5.49	—

[a] Data of Doll, Morgan, and Speizer (*2*) by permission.

The actual causal agent in this factory was not determined because measurement of exposure was not sufficiently defined. Inferences had to be made from the refining process being used and from anecdotal information that in the post-World War I period, in portions of the factory, dust levels were so high they caused employees "not to be able to see their hands in front of their faces." Fortunately, from a public health perspective, the risk of nickel-related nasal cancer appears to be confined to those who had these very high occupational exposures.

Estimation of exposure for less dramatic increases in risk of respiratory cancers is a critical factor for defining the importance of those exposures. Very sophisticated technology can be used to make current measures of exposure in most environmental settings. However, the exposure that is relevant and of interest is that which occurred some 25 to 30 years previously. The extrapolation of information from current measures to previous exposure is not an easy task.

An example of this difficulty was demonstrated in an effort to estimate diesel exhaust exposure in a group of railroad workers thought to be at excess risk from polycyclic hydrocarbon (PCH) exposure in the repair sheds of railroad yards. Because of the availability of both personal and area sampling devices, reasonably reproducible measurements of PCH extractable, respirable particulates in several railroad repair sheds, which had not changed their structural configuration in over 25 years, were able to be made. However, when previous data with which to compare results were sought, it was found that for respirable particulates virtually none were available. What was found was that NO_2, another byproduct of diesel fuel combustion, had been measured in a number of repair sheds in the 1950s and 1960s. Although the earlier NO_2 data are sparse, and the techniques for measurements were unspecified and sampling was not done in the same places, it does appear that there has been a 4- to 8-fold decline in exposure over the last 30 years as determined by NO_2 (Table 3). Thus, when one considers the levels of exposure to PCH meas-

Table 3. Historical NO_2 measurements in parts per million of air in railway repair sheds.[a]

Dates	Number of samples	NO_2, ppm Mean	S.D.	Median
1950–59	19	0.83	0.86	0.4
1960–69	10	0.63	0.41	0.5
1980s	238	0.11	0.10	0.1

[a] Personal communication from T. Smith et al.

ured today in these similar environs, the previous exposures must have been significantly higher, and in the context that there may be a relationship between exposure and disease risk, these higher exposure levels were likely to have been important (Table 4).

A further issue related to exposure estimates is the relationship of exposure to actual dose. Nowhere is this more dramatically demonstrated than in the area of passive cigarette smoke exposure. In experimental studies, relatively sophisticated industrial hygiene technology, which determines room size, air exchange rates, numbers and rates of cigarettes smoked, and measures of effluents from burning cigarettes, has been employed to define levels of exposure. Some of these same techniques have been employed to make similar measurements in office and conference rooms (*3*); in restaurants, bars, taverns, and nightclubs (*4*); in vehicles, and in homes of children with smoking parents (*5*). All of these measures indicate that, depending in large part on the ventilation rate in the particular environmental exposure, levels can be extremely variable. Clearly, none of these measures say anything about dose. Furthermore, in attempting to define dose for population studies, it is clear that whether an individual lives with a smoker currently or over the previous 40 to 50 years, current exposure reveals very little about cumulative dose.

Fortunately, there are techniques to translate current environmental exposure into potentially biologically important dose. Although initial work with carbon monoxide and nicotine has proven disappointing because of the biologically short half-life of these agents, clearly cotinine, a metabolite of nicotine with longer and more stable half-life, is proving to be a useful biologic measure of at least short-term cumulative exposure (*6*). Translating this measurement into a meaningful measure of dose is clearly an area for increased research interest.

Possibly a more direct measure of effective dose is the use of mutagenic assays of urine specimens from exposed and nonexposed subjects. Mutagens have been found in the urine of subjects either experimentally or clinically exposed to cigarette smoke, and these mutagens can be quantitatively related to environmental measures of tobacco smoke byproducts (*7*). Again, relating these relatively short-term exposure-dose relationships to lifelong exposure estimates and risk of respiratory cancer remains a challenge for the future.

Table 4. Estimates of respirable diesel exhaust in the railroad industry.[a]

Job categories	Particulate level, $\mu g/m^3$ National pooled respirable particulate levels[b]	Diesel exhaust population weighted[b,c]	Estimate[d] 1960–69	Estimate[d] 1952–59
Clerks and outside away from train workers	40 ± 4	4	4	4
Engineers, firers	74 ± 3	38	38	38
Brakers, conductors, other train riders	95 ± 4	59	59	59
Shop and repair shed workers	139 ± 5	103	700	700

[a] Personal communication of T. Smith et al.

[b] Based on national pooled weighting of some 511 measurements made in four railroads and weighted by distribution of employees throughout the railroad system.

[c] National pooled data minus background particulate level of 90% of nonexposed (35 $\mu g/m^3$) group.

[d] Based on ratio of mean value of available NO_2 data for the combined period specified, divided by mean values for period 1979–82, rounded off.

Latency, Confounding Factors, and Bias

Thus far, issues related to exposure and dose have been stressed. This is appropriate because the issues of latency, confounding, and bias all hinge on how well exposure can be estimated. As previously indicated, assessment of exposure some 25 to 40 years in the past is important because of the prolonged latency period in the development of respiratory cancers. The risk of lung cancer increases with increasing duration of exposure from time of first exposure. This is dramatically demonstrated by the Doll and Peto analysis (*8*) of the data of Kahn (*9*). These data indicate that for men aged 45 to 74 a 10-year difference in age of starting smoking between ages 15 and 25 may account for the difference in lung cancer rates at ages 55 to 64 and 65 to 74. Furthermore, this duration (age starting) effect may have a greater impact on the rate of lung cancer at ages 55 to 64 than the doubling of the amount actually smoked (Fig. 1). Because most studies of lung cancer deal with people in these older age groups, the misclassification of smokers by not knowing their age of starting smoking and thus their duration of smoking may more than overwhelm the effects of any putative environmental agent under investigation.

Most often, the problem in identifying an environmental hazard, as related to respiratory cancers, is that the relative risk of exposure, particularly for nonoccupational exposures, cannot possibly exceed a 2-fold increase in risk. It is precisely in this relatively low range of excess risk that the epidemiologist has the most dif-

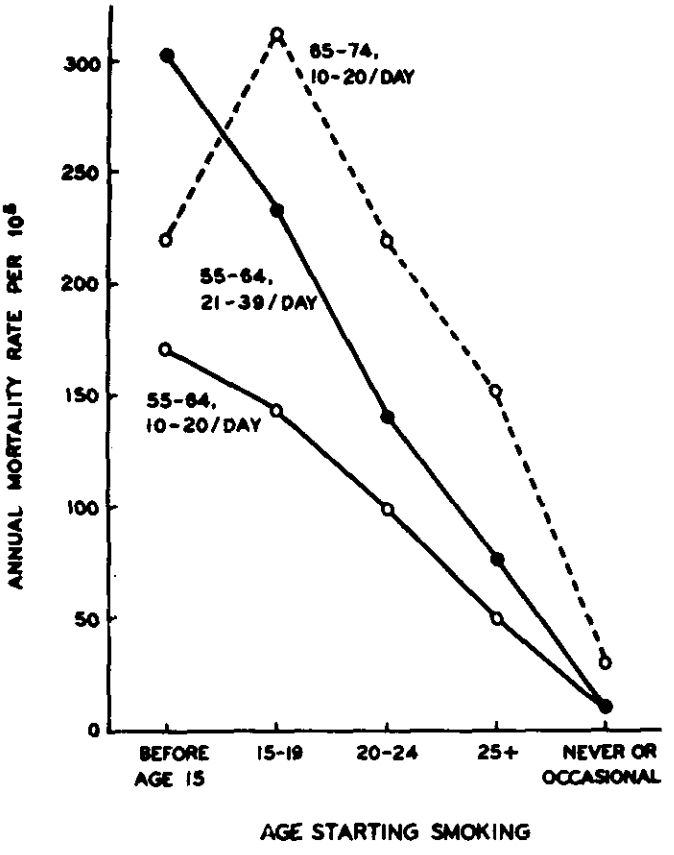

FIGURE 1. Effect of age of starting smoking and amount smoked on annual mortality rate from lung cancer, U.S. men 1954–62. The rate for before age 15 for the 55- to 74-year-olds is based upon six cases, the smallest number for any point in the figure. Figure after Doll and Peto (*8*).

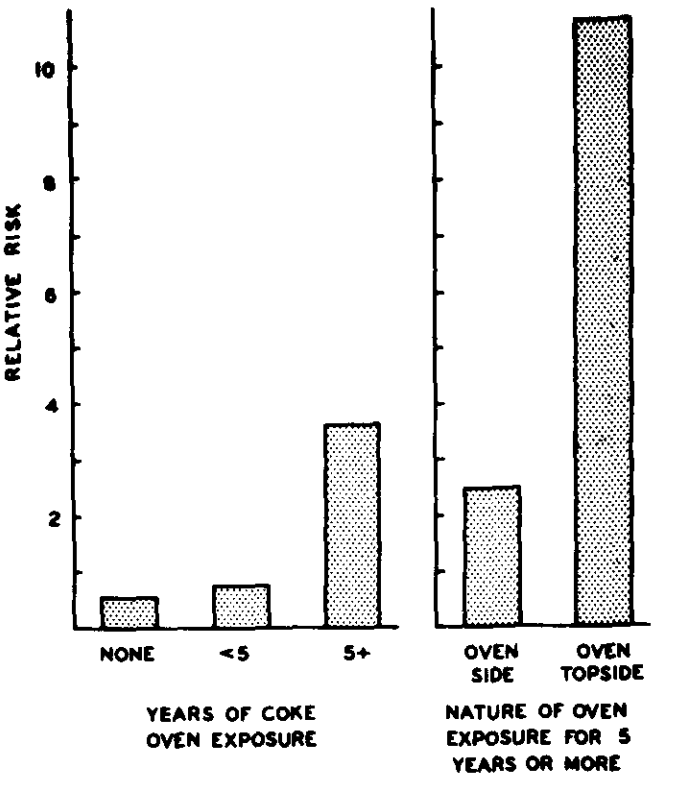

FIGURE 2. Relative risk of lung cancer in steel workers by exposure to coke ovens. Data of Redmond et al. (*11*).

ficulty of being sure that the risk cannot be explained by unidentified confounding factors or bias introduced by misclassification of either exposure or outcome. Most often, only a relatively small proportion of the population actually has had significant exposure to the particular putative agent. Thus, the attributable risk of necessity must be relatively small. For example, in assessing the risk of exposure to fossil fuel combustion products, the available epidemiologic data in the United Kingdom suggest that workers exposed to retort gas plant emissions suffer a relative risk of lung cancer on average approximately 2-fold more than those workers with similar smoking habits not exposed (*10*). Similar studies in the United States of coke oven workers in the steel industry suggest a 2.5- to 10-fold excess risk among the most heavily exposed workers (*11*). In the coke oven studies, there appears to be a dose-response relation related to both duration of exposure and "dose" (Fig. 2).

As exposure becomes less severe, however, the opportunity of detecting an effect becomes increasingly more difficult. Roofers exposed to fossil fuel combustion products at significantly lower levels than retort house workers showed only a 45% excess risk with 20 or more years of exposure, which approached only a 3-fold excess after 40 years of exposure (Fig. 3) (*12*).

Thus, it is apparent that when one moves from these rather intense occupational exposures to more general environmental exposures, the chance of detecting a significant excess relative risk becomes more difficult. On the other hand, because the general population that might be exposed, albeit to lower orders of magnitude than the working population, is so large the attributable risk of disease may very well be a small but nonzero number that should be of public health concern.

Extrapolation from Animals to Humans

A detailed discussion of the various kinds and uses of short-term laboratory studies of environmental carcinogens is beyond the scope of this overview. However, it is important to point out that animal studies are an important part of our armamentarium in the study of environmental agents and respiratory cancer. There are several kinds of short-term laboratory tests that contribute significantly to both an understanding of the biologic mechanisms that lead to tumor formation and identification of particular classes of potentially hazardous environmental compounds. The use of such compounds may need to be restricted, and exposure of humans needs to be assessed to identify the magnitude of

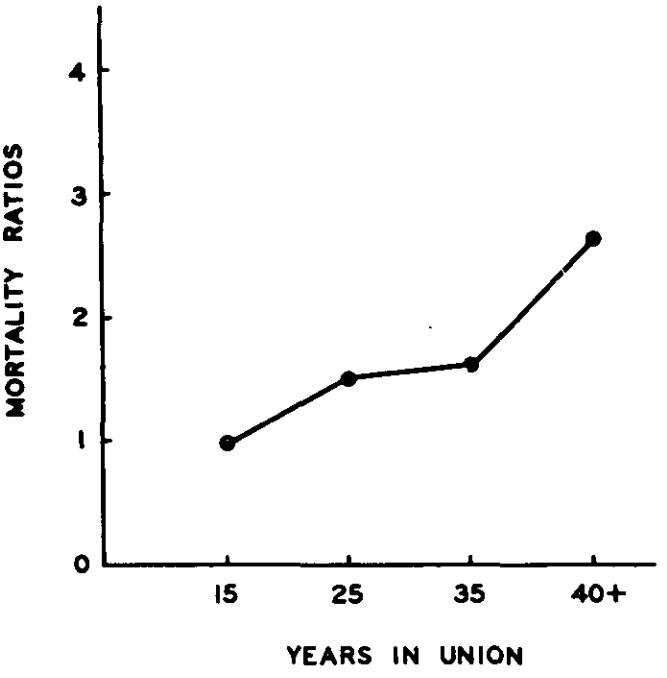

FIGURE 3. Lung cancer mortality ratios by years in roofers' union. Data of Hammond et al. (*12*).

population exposure and whether a risk of disease has been manifest.

The difficulties in extrapolating from short-term assays to human populations are made obvious by comparing the relative ranking of the potency of any given agent. For example, when considering the effects of fossil fuel combustion products in a variety of test systems (*13*), a relative ranking of potency for a number of putative agents can be constructed (Table 5). Although there is relative agreement by rank of the normalized data in both the mutagenic and carcinogenic assays, when these results are compared to those obtained in human population studies, it is apparent that the rankings are quite different. Mechanistically, this means that in humans the exposure-response model cannot be explained by a one-hit, single-process model, and thus extrapolation from even the most carefully conducted studies must be interpreted cautiously. This will surely be important, particularly in regard to fossil fuels and formaldehyde.

Table 5. Relative rankings of potency of effects as measured in different systems.[a]

Assay	Potency
Mutagenic assays	
Bacterial mutagene	Coke > roof tar > cigarette
Mammalian cell	Roof tar > coke > cigarette
Sister chromatid exchange	*Roof tar > coke > cigarette*
Carcinogenic assays	
Viral enhancement	Roof tar > coke > cigarette
Tumor initiation	Coke > roof tar > cigarette
Human epidemiologic studies	Cigarette >>> coke >> roof tar

[a] Modified from Nesnow and Lewtas (*13*) and Speizer (*19*).

Of the agents discussed in the following papers, formaldehyde is a prototype of an agent determined to be a respiratory carcinogen in laboratory animals (*14*). The exercise of reviewing the knowledge gained in the last 5 years about formaldehyde in relation to, first, the available laboratory data and, second, estimates of the magnitude of human exposure and evidence of human risk should provide insights on how well or how poorly one can extrapolate from animal data to humans.

Population at Risk

Assessing the impact of exposure to radon, determining who is at risk and by how much, is very complex. There is no question that radioactive agents interact with cigarette smoking to increase synergistically the risk of lung cancer (*15*). The question is the degree to which exposure to radon in the natural setting increases the risk of lung cancer.

Sources of radon indoors are reasonably well understood. The main radon product (radon-222) results from the decay series from uranium-238. The immediate precursor to radon-222 is radium-226. Therefore, the amount of radium in earth materials determines the availability of radon that might be emitted as a gas. When this gas is emitted outdoors, it is widely dispersed and concentrations are trivial. If the contaminant enters a building either directly as a gas or by being emitted from porous building material containing radium, the indoor concentration may rise, depending upon the ventilation rates indoors and the size of the space into which the gas is emitted.

Radon has a 3.8 day half-life, and the immediate decay products form molecular-sized particles that rapidly diffuse and attach to other solid particles or water droplets in air. There are regional differences in exposure that relate to the level of radium in the soil or in soil-containing building materials. Regional differences have been monitored and suggest that up to 10% of sites in the United States have concentrations indoors of radon levels that exceed (>4 pCi/L) those found in buildings near abandoned uranium mill tailing sites (*16*).

In some countries (e.g., Sweden), as many as 80% of the homes tested had levels that exceeded 4 pCi/L. Whether this level of 4 pCi/L represents an important cutoff point relates to information obtained from studies of uranium miners. Samet et al. (*17*) showed that Navajo men who had worked in uranium mines had a significant risk of lung cancer that appeared to be independent of cigarette smoking. Because smoking rates were so low in this study, it is interesting to speculate that the 9 of 32 who did not have an occupational exposure to radon may very well have experienced community exposure sufficient to contribute to their risk for lung cancer.

To make a population estimate of risk requires additional information on not only the distribution on a national scale of concentrations of exposure but also some understanding of how dose is modified by other factors. For example, radioactive decay products can be inhaled and deposited in the airways (*18*). The dep-

Table 6. Estimates of persons exposed to ≥4 pCi radon by presence or absence of smokers in the household.[a]

	Percent of all households	No. units/ 100,000	No. units/ total pop. (220×10^6)	Estimated no. persons exposed
Households with at least one smoker	70	24,500	53.9×10^5	161.7×10^5
Households with no smokers	30	10,500	23.1×10^5	69.3×10^5

[a] Data derived from multiple sources (*20*).

osition appears, in part, to relate to the smoking status of the exposed subjects; in general, smokers retained a greater fraction of the inhaled particles than nonsmokers. However, for radon deposition, the dose may relate to the quantity of unattached alpha particles rather than the total number of particles.

If it is assumed that 10% of the homes across the nation have the potential to exceed the level of 4 pCi/L and these levels do indeed increase the risk of lung cancer by some finite amount, one could set up a hierarchy of risk from radon exposure and actually calculate the populations that might be at different levels of risk. For example, if approximately 70% of households contain at least one smoker (Table 6), these calculations would suggest 6.9×10^6 people would be at risk of pure radon exposure without enhancement of that risk by exposure to cigarette smoke. Obviously, such estimates are crude to start with and involve a number of assumptions that would require additional research to validate. This example is offered only to demonstrate the complexity as well as magnitude of the problems in estimating populations at risk.

Estimates such as these need to be determined not only for radon but for other agents as well. The data sources require critical evaluation. Where acceptable data are lacking, potential sources for new data need to be identified. Where methodologies need to be developed for pooling multiple sources of information, the kinds of risk estimates that should be made must be suggested.

Attributable Risk

Although for each of the agents discussed, the absolute attributable risk will of necessity not be large, lung cancer kills more than 100,000 people annually and is the major form of cancer in both sexes in middle age. Therefore, even very modest percentages of attributable risks to each agent would have significant impact both medically and economically on the health of the nation. The degree to which these agents interact with cigarette smoking and contribute, therefore, to the upwards of 90% of lung cancer that is related to smoking may be an important aspect of quantifying the effects of these agents. To the degree that these agents act synergistically with smoking, then the reduction of smoking or the reduction of exposure to these agents may have much greater public health consequences than would be anticipated from the directly measured attributable risk of each of these agents separately.

Table 7. Levels of "attributable risk" of lung cancer to air pollution over a 25-year period.

Year of estimate	Comment	Reference
1955	Urban air adds approximately 100 deaths/100,000	(*21*)
1972	5% of all lung cancer	(*22*)
1973	5% increase of pulmonary cancer for each increase of 1 μg/1000 m^3 of benzo(a)pyrene	(*23*)
1976	Possibly a tenth of the effect of cigarette smoking	(*24*)
1976	0.4 death/100,000 per μg/1000 m^3 benzo(a)pyrene in nonsmokers; 1.4 deaths/100,000 per μg/1000 m^3 benzo(a)pyrene in smokers (in U.S. 1 cigarette/day is equivalent to 10 μg/1000 m^3 benzo(a)pyrene)	(*25*)
1978	5–10 cases/100,000 persons acting together with cigarette smoking	(*26*)
1981	1%–2% of lung cancer; less than 1% of all cancers in the future	(*8*)
1983	Nonzero; less than 2% lung cancers	(*19*)

With increasing sophistication and more careful assessment of existing data, the estimates of the attributable risk for lung cancer from general environmental agents over the last 25 to 30 years have been reduced by a factor of almost 10 (Table 7). In each case, including the most recent by this author, each of these estimates is flawed by lack of sufficient data or information about a number of the issues discussed above. In all cases, however, no risk assessor would state that the risk is zero, and in none of these estimates are either the risks from occupational exposures or from radon considered, each of which could be contributing significantly to lung cancers occurring in nonsmokers and modifying the risk in smokers. Thus, it becomes our task to assess the risks that result from human activity as well as exposure that occurs naturally and, to the degree possible, weigh the risks and benefits of these activities, not only in terms of dollars, but in terms of human values. Where possible, alternatives must be identified that may further reduce risks.

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